REMARKS

This Amendment is in response to the Office Action dated July 30, 2002. Claims 1–46 are pending in the above-identified application. Claims 2, 10, 18, 20, and 44–46 are amended. Claims 47-55 have been added. Claim 17 is cancelled. No new matter has been added to this application by way of amendment or addition of new claims.

PRELIMINARY MATTERS:

The Examiner objects to claim 2 because of a misspelling of the term "heparin." The omission of a space between "heparin" and "in" has been corrected, and Applicants respectfully request the Examiner withdraw this objection to claim 2. Likewise, misspellings of "polysaccharide" in claims 2 and 10 have been corrected.

Claims 47-55 have been added in this Response. These claims recite methods of treatment or prevention of multiple conditions such as treatment and prevention of the proliferation of smooth muscle cells, angiogenesis, a method of use as a neuroprotective agent, and as a medicament using the compositions and methods of the invention. These claims are supported by paragraphs 35–36 of the specification as filed and thus do not add new matter to the specification.

REJECTIONS UNDER 35 U.S.C. § 112:

The Examiner rejects claims 44–46 under 35 U.S.C. § 112, second paragraph, as allegedly "being incomplete for omitting essential elements, such omission amounting to a gap between the elements." Applicants respectfully traverse this rejection, however, for the purpose of furthering prosecution, Applicants amend claims 44–46 to recite "a method of treating arterial thrombotic accidents or venous thrombosis

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in a patient in need of such treatment." Reconsideration and withdrawal of this grounds of rejection of claims 44–46 is therefore respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103(A):

The Examiner rejects claims 1–5, 7–17, 21–24, 26–36, and 38–46 under 35 U.S.C. § 103(a) as unpatentable over Mardiguian (AU-B-70519/81) in combination with Mardiguian (U.S. Patent No. 6,384,021), Mardiguian (U.S. Patent No. 4,440,926), Galezowski et al., "Homoconjugated hydrogen bonds with amidine and guanine bases," J. Chem. Soc. Faraday Transactions 93(15):2515–2518 (1997), and Weitz et al. (U.S. Patent No. 6,075,013). Applicants traverse this rejection for the reasons set forth below.

The Examiner has not made a *prima facie* showing of obviousness of the claimed invention. In order to establish a *prima facie* showing of obviousness the Examiner must show that: (1) there is some suggestion or motivation in the cited references or in the relevant art to combine the teachings; (2) there is a reasonable chance of success in combining the teachings of the references; and (3) the references teach all of the claim limitations. *See* MPEP §§ 706.02(j); 2142–43. The Examiner has not made a *prima facie* case of obviousness of the present invention because there is no motivation to combine the cited references and these references do not teach all of the elements of the rejected claims. In rejecting these claims as obvious over the teachings of the above-cited references, the Examiner states:

> It is obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings given above and come up with a method of producing low molecular weight heparin as instantly claimed with a

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> reasonable amount of success. All the necessary steps to produce low molecular weight salt of sulphated polysaccharide of heparin seems to be set forth in the prior art above.
>
> . . .
>
> An artisan with ordinary skill would be motivated to do so because the reagents and conditions used are mild and lead to the desired degree of polymerization and yield a product which has an optimum composition, regulated by operating conditions, according to average molecular weight desired.

First, the Examiner has not established the motivation in the references or the relevant art to combine the reference teachings. The Federal Circuit has repeatedly stated that to make out a prima facie case of obviousness, there must be particular findings as to the reason why "the skilled artisan, with no knowledge of the claimed invention, would have selected these compounds in the manner claimed." *In re Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002) (emphasis added) (quoting *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000)). The Examiner has not provided particular findings as to why a skilled artisan, without the benefit of knowledge of Applicants' invention, would have specifically chosen the claimed compositions, with the recited physical and biological properties, and the claimed methods. Without such findings, the Examiner has failed to establish motivation to combine with a reasonable expectation of success and is instead engaging in impermissible hindsight reconstruction of the claimed invention.

In addition, the cited art does not disclose all of the elements of the rejected composition and method claims. Compositions of claim 1 comprising at least one alkali or alkaline earth metal salt of at least one sulphated polysaccharide of heparin having a

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mean molecular weight of 1500-3000 and anti-Xa activity in the range from 94-150 IU/mg, anti-IIa activity in the range up to 10 IU/mg, and a ratio of anti-Xa:anti-IIa activity of greater than 10:1, are not disclosed in any of the cited references.

Mardiguian (AU-B-70519/81) describes alkali or alkaline earth metal salts with a ratio of anti-Xa : anti-IIa activity of only 2-10:1 on page 7, Table A, as noted by the Examiner. Also, Mardiguian (U.S. Patent No. 6,384,021), does not demonstrate a process that produces low molecular weight heparins that have the high anti-Xa activity seen in Applicants' examples 3, 5, 6, and 8—anti-Xa activity ranging from 134 to 149. Specifically, a person skilled in the art, using the disclosure of U.S. Patent No. 6,384,021, would not be able to produce compositions with an anti-Xa activity above 120. *See* U.S. Patent No. 6,384,021, examples 1–5. Notably, the Examiner did not reject claim 6, which recites a composition according to claim 2 having an anti-Xa activity in the range of 140 to 150 IU/mg and a mean molecular weight in the range of 2000 to 3000 daltons. The other references cited likewise fail to disclose compositions with all of the biological and chemical properties recited in claim 1.

The references also fail to disclose the claimed compositions wherein the sulphated polysaccharide of heparin has 2 to 26 saccharide units and has a 4,5-unsaturated glucuronic acid 2-O-sulphate at least one end. The "sulphated polysaccharide of heparin" of the present invention is closely tied to the method of making the claimed compositions. And the references fail to disclose all of the steps of the method of making the claimed compositions which are set forth in claims 10, 26, and claims dependent thereon.

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A change or slight variation in the method of preparing the compositions of the present invention, e.g., a change in the base properties, gives rise to the risk that the compounds obtained would be a mixture of polysaccharides with different physico-chemical and biological features than those claimed in the present application. The relationship between the method of producing a heparin-related compound and the final product obtained is well-established in the art. *See, e.g.*, Robert J. Linhardt, et al., Oligosaccharide Mapping of Low Molecular Weight Heparins: Structure and Activity Differences, J. Med. Chem., 33:1639–1645, 1643 (1990) (attached for the Examiner's convenience as Appendix II). It is also known in the art that the process used in depolymerization of heparins makes a difference in the molecular weight, degree of sulfatation, and the physical and biological properties of the resulting compounds. *See, e.g.*, U.S. Patent No. 6,384,021, Col. 1 ll. 19-35. Small changes in the processes of making heparin derivatives and analogs can make them bioinequivalent.

Mardiguian (AU-B-70519/81) does not teach purification using hydrogen peroxide, a mole ratio of the base to the quaternary ammonium salt of the benzyl ester of heparin of 0.2:1 to 5:1 and a degree of esterification from 50-100%. It does disclose use of the organic base 1,5-diaza-bicyclo[4,3,0]5-nonene for the depolymerization step. But Applicants note that the Mardiguian reaction is carried out at 60° C (examples 16 and 17) while the depolymerization step of the present invention is carried out at a temperature ranging from -20° C to 40° C (*see* Specification ¶¶ 22, 27). And the low molecular weight heparins obtained by the process disclosed in AU-B-70519/81 have a molecular weight of 4200 and 5500 and display high anticoagulant activity outside the range of the claimed compound *in vitro*.

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Mardiguian (U.S. Patent No. 6,384,021), also fails to teach the depolymerization step of claim 10, as amended, using a base with a pKa over 20 and does not teach the purification step, a mole ratio, and the degree of esterification of the quaternary ammonium salt of the benzyl ester of heparin. For example, this patent describes a different process of depolymerization using Triton B (examples 1, 2, 4), whereas the method of preparing the claimed compounds of the present invention describes use of a strong bases such as guanidine or phoshazene bases (Specification ¶¶ 20, 25). And, as stated above, it is known in the art that slight variation in the process would lead to heparin compositions with different chemical and biological attributes.

Mardiguian (4,440,926) lacks the same three aspects of the claimed process. This reference also discloses use of a different base (1,5-diazabicyclo[4.3.0]non-5-ene) than is used in the present invention *See* U.S. Patent No. 4,440,926, Col. 5 ll. 2-6. There is no indication that the compounds that would be produced by this base would have the claimed chemical and biological features of the present invention. Additionally, U.S. Patent No. 4,440,926 is directed to the preparation of esters of heparin but does not disclose or suggest low molecular weight heparins produced by use of the disclosed organic base. This patent is almost 20 years old—if the preparation of the claimed composition with the claimed physical and biological properties was obvious with use of this base for depolymerization, the present invention would have been discovered sooner.

Likewise, Weitz et al. (U.S. Patent No. 6,075,013) does not teach use of the bases of the present invention for depolymerization—Weitz teaches use of alkaline, nitrous acid, and enzymatic depolymerization with heparinase at Col. 8, ll. 52–63.

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Given the chemical and biological differences between the compounds produced using 1,5-diaza-bicyclo[4,3,0] 5-nonene and the compounds produced and claimed in the present invention, it would not be obvious to one of ordinary skill in the art to use an organic base with a pKa greater than 20 in the depolymerization step of the claimed method, nor to use the specific organic bases of 1,5,7 triaza-bicyclo-[4,4,0] dec-5-ene, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine, a guanidine base, or a phosphazene base. Therefore, the composition claims directed toward sulphated polysaccharides of heparin and method claims 10, 26, and the dependent upon these claims are not obvious to one of ordinary skill upon review of these references.

Because there is no motivation to combine the cited references and because these references do not teach or suggest the claimed compositions or teach or suggest the claimed method to produce compounds with the claimed physical and biological activities, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1–5, 7–16, 21–24, 26–36, and 38–46 under 35 U.S.C. § 103(a).

OBJECTIONS:

Claims 6, 18, 19, 20, 25, and 37 stand objected to because they depend from independent claims that have been rejected. Applicants respectfully request that these objection be withdrawn in light of Applicants' remarks regarding the claim rejections under 35 U.S.C. § 103(a).

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In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this Application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: December 20, 2002

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APPENDIX I

AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE PURSUANT TO 37 C.F.R. § 1.121(c)(1)(ii)

2. (Amended) A composition comprising at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide [polysaccaride] of heparin in [heparinin] which the alkali or alkaline-earth metal salt of at least one sulphated polysaccharide [polysaccaride] of heparin has 2 to 26 saccharide units and has a 4,5-unsaturated glucuronic acid 2-O-sulphate unit at at least one end.

10. (Amended) The method of preparing at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide [polysaccaride] of heparin comprising:

depolymerizing a quarternary ammonium salt of the benzyl ester of heparin in an organic medium with a base with a pKa greater than 20;

converting the quarternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt;

saponifying the ester; and

optionally purifying the product;

wherein said base is 1,5,7 triazabicyclo-[4.4.0]-dec-5-ene, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine, a guanidine base, or a phosphazene base.

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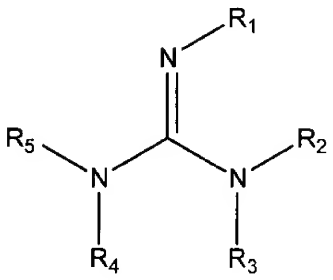
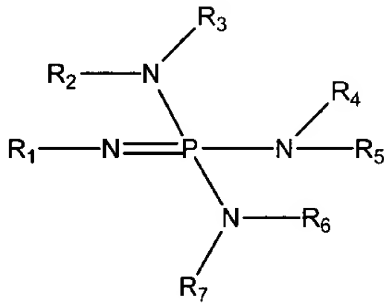
18. (Amended) The method according to claim 10 [17], in which the base of guanidine comprises:



where R_1 is hydrogen or alkyl, and where R_2, R_3, R_4, and R_5, which are identical or different, and each is a C_1-C_6 alkyl.

20. (Amended) The method according to claim 10 [17], in which the base of phosphazene comprises:



where R_1 to R_7 are identical or different, and each is a C_1-C_6 alkyl.

44. (Amended) A method of treating arterial thrombotic accidents or venous thrombosis in a patient in need of such treatment [a patient] comprising the administration of a solution of a pharmaceutical composition by the subcutaneous,

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intramuscular, intravenous, or pulmonary route, in which a composition according to claim 2 is an active ingredient present in an amount efficacious for such treatment.

45. (Amended) A method of treating arterial thrombotic accidents or venous thrombosis in a patient in need of such treatment [a patient] comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition produced by the method according to claim 10 is an active ingredient present in an amount efficacious for such treatment.

46. (Amended) A method of treating arterial thrombotic accidents or venous thrombosis in a patient in need of such treatment [a patient] comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition produced by the method according to claim 26 is an active ingredient present in an amount efficacious for such treatment.

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